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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,351	06/07/2002	Stace Lindsay	06727/008002	8638

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GTC BIOTHERAPEUTICS, INC.
175 CROSSING BOULEVARD, SUITE 410
FRAMINGHAM, MA 01702

EXAMINER	
BERTOGLIO, VALARIE E	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 03/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,351	LINDSAY ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *2,4,8,9 and 12-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-7,10 and 11* is/are rejected.

7)☒ Claim(s) *11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *05/02 & 05/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' supplemental election received 01/14/2005 has been entered.

Applicant's election with traverse of Group III in the supplemental reply filed on 01/14/2005 is acknowledged. The traversal is on the ground(s) that the claims of Groups I and III are so linked as to form a single general inventive concept. Applicant argues that the nucleic acid cannot function in certain commonly used cell lines as it is designed to be expressed in mammary tissue. In response, isolated mammary gland epithelial cells utilize mammary specific promoters and the claimed nucleic acid could be expressed in these cells, in vitro. Therefore, the nucleic acid of Group I has multiple uses, including in vitro cell assays and in making a transgenic animal. However, as it would not require undue burden to search the claimed nucleic acid with the claimed mammals, Groups I and III are rejoined.

Applicants have not provided arguments regarding the restriction requirement between Groups IV-VI and the restriction is maintained for reasons of record.

Claims 2,4,8,9,12-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claim 5 contains subject matter drawn to a non-elected invention. Claim 5 will only be examined as it relates to the elected invention.

Claims 1-20 are pending. Claims 1,3,5-7,10 and 11 are under consideration in the instant office action.

Specification

The disclosure is objected to because of the following informalities: At page 12, line 25, the specification references a WO document as WO 96/2287. This number appears to be

incomplete and to be a typographical error. The WO document of Murgita that was published in 1996 is WO 96/22787.

Appropriate correction is required.

Claim Objections

Claim 11 is objected to because of the following informalities: Claim 11 depends from the method of claim 10, however, claim 11 as worded, is not an active method step. As written, claim 11 limits the rHuAFP contained in the milk collected in step (c) of claim 10 to rHuAFP purified from said milk. If the milk is just collected, then it cannot contain rHuAFP that has been purified from itself. Appropriate correction is required.

Claim Rejections - 35 USC § 112-1st paragraph

1) Claims 3,5,7, 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a non-human transgenic mammal whose genome comprises a transgene that results in expression of rHuAFP in mammary epithelial cells, does not reasonably provide enablement for a chimeric mammal wherein only a variable portion of the cells of the animal comprises a transgene that results in expression of rHuAFP in the mammary epithelial cells wherein the rHuAFP is secreted into the milk of the mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404).

Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Claims 3,5,7, 10 and 11 are so broad as to encompass both transgenic mammals whose somatic and germ cells comprise the claimed transgene as well as chimeric mammals wherein a variable portion of the cells of the animal comprises the claimed transgene.

The specification is not enabling for the chimeric mammals encompassed by the claims. The specification teaches how to make stable transgenic non-human mammals whose genome comprises the claimed transgene. The specification fails, however, to teach how to make a chimeric mammal such that a detectable level of rHuAFP is secreted into the milk. The art at the time of filing was such that the skilled artisan could predictably make the claimed non-human mammals wherein the somatic and germ cells of the non-human mammal comprise the transgene. Numerous transgenic farm animal species had been made expressing various transgenes in milk of stable transgenic animals (DeBoer, US 5,633,076, IDS; Clark, US 5,322,775, IDS; Lubon, US 5,831,141, IDS). However, similar results have not been reported for

chimeric animals. The resulting phenotype of such chimeric mammals is not predictable as it is inherent in the technique that the number and identity of the cells carrying the transgene cannot be predetermined. Such a method does not allow for the direction of the transgene to mammary epithelial cells and does not allow for control of the number of mammary epithelial cells that will receive the transgene. Without such control, it cannot be predicted that any given chimeric mammal will express the transgene and secrete any detectable level of rHuAFP into the milk of the mammal.

Given the lack of guidance with respect to how many mammary epithelial cells must express the claimed transgene to allow for detectable levels of cells in the milk of the claimed mammals, as well as how to attain a chimeric mammal expressing, at a sufficient level, the transgene in that necessary number of mammary epithelial cells, the skilled artisan would not know how to make the chimeric mammals encompassed by the claims. It would require undue experimentation for the skilled artisan to determine how to make the claimed chimeric mammals encompassed by the claims such that detectable levels of rHuAFP are secreted into the milk of the animal.

2) Claims 10 and 11 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a rHuAFP that is secreted in the milk of a transgenic non-human mammal wherein the non-human mammal is made by introducing the transgene into cells of an embryo and for a method of producing a rHuAFP that is secreted in the milk of a transgenic mouse wherein the mouse is made by introducing the transgene into cells of an embryo or into mouse ES cells, does not reasonably provide

enablement for any such mammal made using any cell type or a transgenic human made using any method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Claims 10 and 11 broadly encompass transfecting any type of cell with a transgene and growing that cell to make a mammal. The specification teaches microinjecting cells of an embryo and developing the embryo to form a chimeric animal that can be bred to form true germline transgenic animals (page 13, lines 10-15). The specification also teaches introducing

transgenes into ES cells and generating chimeric animals through blastocyst transfer (page 13, line 21–page 14, line 1) or through nuclear transfer (page 14, lines 2-8). The specification does not offer specific guidance with respect to using any cell type in blastocyst transfer or to nuclear transfer.

The state of the art at the time of filing held that not all cell types will give rise to a mammal when transplanted into a blastocyst. Totipotent ES cells that can contribute to the germline following introduction into a blastocyst were not known in the art at the time of filing for any species other than mouse. Wheeler (2001, Theriogenology, Vol. 56, 1345-1369) taught putative pig ES cells, which produced pig chimeras but there is no disclosure that the chimera gave rise to a pig of the ES cell phenotype (pages 1351-1352). Further, Wheeler states, in reference to ES cells recently isolated and the production of swine and cattle chimera, "validation of totipotency of these embryo-derived ES cell lines awaits conformation" (page 1351, parag. 1, last sentence). Prelle (1999, Cells Tissues Organs, Vol. 165, pages 220-236) states many embryo-derived cell lines resemble morphologically mouse ES cells, and have the ability to differentiate in vitro, but there is no evidence of live born, fertile germ line chimeras in species other than mouse (page 222, col. 2, parag. 1, lines 10-16). Moreadith (1997, Jour Mol Med, Vol. 75, pages 208-216) states several putative ES cell lines had been isolated from hamster, pig, sheep, cattle, rabbit, rat, mink, monkey and humans, but Moreadith also states that the technology in was limited to mice (page 214, col. 1, parag. 3, lines 5-12). Therefore, the art at the time of filing held that non-mouse totipotent ES cells capable of contributing to the germline and forming a stable transgenic animal were not known.

With respect to the general and prophetic suggestion of using nuclear transfer to generate the mammals of the invention, the state art of nuclear transfer at the time of filing held that the technique was highly underdeveloped and unpredictable. The first report of gene targeting to introduce the COL1A1 locus into the genome of sheep utilized transfer of nuclei fetal fibroblasts (McCreath, 2000, Nature, Vol. 405, pages 1066-1069) revealed abnormal transgene expression/function. Furthermore, cloned fetuses, irrespective of whether they are genetically modified, are often abnormal and nonviable with no consistent pattern of abnormality to indicate the cause of the defects (Dinnyes, Cloning and Stem Cells, Vol. 4, pages 81-90, specifically page 87, column 1, 3rd full paragraph; McCreath, paragraph bridging pages 1067 and 1068). It would be difficult to determine whether the phenotype resulting in a genetically modified animal generated by somatic cell nuclear transfer is a result of the genetic modification or an artifact of the nuclear transfer technique. Attempts to use nuclear transfer to obtain transgenic goats expressing recombinant human antithrombin III in the mammary glands did meet success, however, this was reported after Applicant's effective filing date of January 06, 1999 (Baguisi, May 1999, Nature Biotechnology, Vol. 17, pages 456-461). Thus, at the time of filing, the technique of nuclear transfer was highly underdeveloped, success appeared to be species specific and the phenotype resulting from genetic modification of cells prior to nuclear transfer was highly unpredictable and difficult to discern.

The specification fails to provide any guidance with respect to totipotent ES cells for non-mouse species or with respect to the unpredictability and underdeveloped nature of the art associated with nuclear transfer. Without such guidance, it would require undue experimentation for the skilled artisan to determine how to overcome the underdeveloped and unpredictable state

of the art so as to make a transgenic mammal using any transfected cell type as required and encompassed by claims 10 and 11.

Claims 10 and 11 also encompass a method of producing a rHuAFP by making a transgenic human expressing the protein in its milk. The art at the time of filing held that expression of recombinant (transgenic) DNA in humans was unpredictable and that transgenesis in primates in general was a highly underdeveloped art (refer to Wolfgang, 2002, Molecular Reproduction and Development, Vol. 62, pages 69-72, specifically Abstract, lines 1-8; page 69, col. 2, paragraph 2; page 72, col. 1, paragraph 3). The underdeveloped art of making transgenic humans is further complicated by transgene silencing as a result of position effects in human cells (Sutter, 2003, PNAS, Vol. 100, pages 1105-1110; Kanduri, 2002, Cancer Res, Vol. 62, pages 4545-4548), especially at the ends of chromosomes (see Baur, 2001, Science, Vol. 292, pages 2075), making the expression of the transgene variable and unpredictable. For example, Sutter demonstrated the silencing of a reporter transgene in human K562 cells (page 1105, col. 1, para 2; page 1107, col. 1). Furthermore, there is no art or evidence of record indicating that a transgenic human has ever been made. The specification 4erfails to provide guidance as to how to overcome the underdeveloped nature of primate transgenesis and transgene silencing in human cells to make a transgenic human expressing a recombinant protein into the milk of the human as encompassed by the claims. Therefore, it would require undue experimentation to determine how to express a rHuAFP transgene in the mammary gland of humans to produce rHuAFP that is secreted into the milk of the human. Limiting claim 10 to non-human mammal would overcome this aspect of the rejection.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 5 recites the limitation "non-human transgenic mammal of claim 1 or 2" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 5 is drawn to the non-human transgenic mammal of claim 1 or 2. However, claims 1 and 2 are both drawn to nucleic acids, not non-human transgenic mammals.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1,3,5-7,10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deboer (1997, US 5,633,076; IDS) or Clark (1994, US 5,322,775;IDS) or Lubon (1998, US

5,831,141; IDS) in view of Morinaga (1983, PNAS, Vol. 80, pages 4604-4608; IDS) and Bennett (1997, Breast Cancer Research and Treatment, Vol. 45, pages 169-179; IDS).

Claim 1 is drawn to a nucleic acid encoding rHuAFP, a milk-specific promoter and a leader sequence encoding a protein secretory signal. Claim 3 is drawn to a non-human transgenic mammal expressing rHuAFP in its milk wherein the milk producing cells of the mammal contain a transgene encoding the nucleic acid as set forth in claim 1. Claim 5 limits the mammal of claim 1 to a goat, cow, sheep or pig. Claim 1 is not drawn to a mammal; however, claim 5 is being examined as though it limits the mammal of claim 3, as this is the only preceding claim drawn to a mammal. Claim 6 is drawn to non-human milk comprising rHuAFP. Claim 7 is drawn to the milk of claim 6 wherein the milk is produced by a non-human transgenic mammal as set forth by claim 3. Claim 10 is drawn to a method of making rHuAFP that is secreted in the milk of a mammal by transfecting a cell with the above described transgene, growing the cell to produce a mammal and collecting the milk from the mammal. Claim 11 comprises the additional step of purifying the rHuAFP from the milk.

Deboer taught generating transgenic cows and mice using transgenes encoding human serum albumin (see Example 10), human lactoferrin (see Example 5) or human lysozyme (see Example 22) operably linked to the αS1 casein promoter (see Example 5) or β lactoglobulin promoter (see Example 20) and a signal sequence (see Examples 4 and 5 for hLF and Example 10 for hSA) by microinjecting transgene constructs into the pronuclei of fertilized oocytes or into the nuclei of each of 2 blastomeres of a 2-cell embryo (see col. 33, line 48-col. 34, line 10), which are cells as required by claim 10. The embryos were grown to generate mammals who later express the recombinant protein in the milk. Deboer also taught purifying hSA from the

milk (Example 11). Inherently, to purify or determine presence of a protein in milk, the milk must be collected as required by claim 10. The teachings of DeBoer include milk derived from the mammals as required by claims 6 and 7.

Clark taught generating transgenic sheep and mice using a transgene encoding Factor IX operably linked to the β–lactoglobulin promoter and a signal sequence (col. 29, lines 23-44 and 50-55) by microinjecting transgene constructs into the pronuclei of fertilized oocytes or into the nuclei of each of 2 blastomeres of a 2-cell embryo (see col. 15, lines 29-31), which are cells as required by claim 10. The embryos were grown to generate mammals that later express the recombinant protein in the milk (see Example 8). Clark also taught collecting (col. 19, lines 21-24) and purifying the protein from the milk (col. 19, lines 29-34). The teachings of Clark include milk derived from the mammals as required by claims 6 and 7.

Lubon taught generating transgenic pigs and mice using a transgene encoding human protein C operably linked to the whey acid protein promoter and signal sequence (col. 11, lines 5-37) by microinjecting transgene constructs into the pronuclei of fertilized oocytes (mouse, col. 12, lines 23-35; pig, col. 12, lines 37-64), which are cells as required by claim 10. The embryos were grown to generate mammals that later express the recombinant protein in the milk (for example see Example 11; Figure 7). Lubon also taught collecting and purifying the protein from the milk (col. 14, lines 8-20;col. 22, lines 35-44). The teachings of Lubon include milk derived from the mammals as required by claims 6 and 7.

Neither DeBoer, Clark nor Lubon taught human AFP as the protein being expressed in the mammary glands of the mammals.

However, Morinaga taught the nucleic acid sequence of AFP (see Figure 2).

Accordingly, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to make the claimed transgenic mammals and milk derived therefrom as taught by each of Deboer, Clark and Lubon wherein the gene expressed and secreted into the milk was the rHuAFP gene as taught by Morinaga. One of ordinary skill in the art would have been sufficiently motivated to replace the various genes of each of Deboer, Clark and Lubon with the rHuAFP gene, as exp0ression of a transgene in the mammary gland was an art accepted means of producing large quantities of recombinant protein. One of ordinary skill in the art would have been sufficiently motivated to produce large quantities of rHuAFP for use in cancer therapy. Furthermore, Bennett taught that recombinant human AFP can effectively bind estrogen and may be a regulator of estrogen-dependent human breast cancer (Abstract, last 3 lines; page 170, col. 1, paragraph 2).

The skilled artisan would have a reasonable expectation of success in combining the teachings of DeBoer, Clark or Lubon with those of Morinaga because it was routine in the art to express a recombinant gene in the mammary epithelial cells of mammals and a vast array of genes had been utilized and expressed successfully.

Thus, the claimed invention, as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Valarie Bertoglio
Examiner
Art Unit 1632

Joe Woitach
AU1632